Contralateral conjugate eye deviation during deep brain stimulation of the subthalamic nucleus

DONALD C. SHIELDS, M.D., PH.D., ALESSANDRA GORGULHO, M.D., ERIC BEHNKE, B.S., DENNIS MALKASIAN, M.D., PH.D., AND ANTONIO A. F. DESALLES, M.D., PH.D.

Division of Neurosurgery, Department of Surgery, David Geffen School of Medicine, University of California, Los Angeles, California

Object. Deep brain stimulation of the subthalamic nucleus (STN) in patients with Parkinson disease is often very effective for treatment of debilitating motor symptoms. Nevertheless, the small size of the STN and its proximity to axonal projections results in multiple side effects during high-frequency stimulation. Contralateral eye deviation is produced in a small percentage of patients, but the precise mechanism of this side effect is at present poorly understood.

Methods. Contralateral eye deviation was produced by high-frequency stimulation of 22 contact sites in nine patients undergoing deep brain stimulation of the STN. The precise locations of these contacts were calculated and compiled in order to locate the stimulated structure responsible for eye deviation.

Results. The mean x, y, and z coordinates associated with contralateral eye deviation were found to be 11.57, 2.03, and 3.83 mm lateral, posterior, and inferior to the anterior commissure–posterior commissure midpoint, respectively. The point described by these coordinates is located within the lateral anterosuperior border of the STN.

Conclusions. Given that stimulation of frontal eye field cortical regions produces similar contralateral conjugate eye deviation, these results are best explained by electrical current spread to nearby frontal eye field axons coursing lateral to the STN within the internal capsule. Thus, placement of the implanted electrode in a more medial, posterior, and inferior position may bring resolution of these symptoms by reducing the amount of current spread to internal capsule axons. (DOI: 10.3171/JNS-07/07/0037)

Key Words • contralateral eye deviation • deep brain stimulation • frontal eye field • internal capsule • subthalamic nucleus

NEURODEGENERATIVE processes of the basal ganglia result in a variety of movement disorders. The most common of these is PD, which affects over 1.2 million individuals in the US. Environmental and genetic factors contribute to a reduction of dopamine levels in the basal ganglia, which can lead to bradykinesia, postural instability, tremors, and rigidity. These and other symptoms can often be improved by levodopa administration; nevertheless, long-term failure of medical therapy in some patients has prompted a resurgence in surgical therapies for PD. High-frequency stimulation of basal ganglia structures via deep brain electrode placement has emerged as an effective treatment for PD symptoms.18 The STN is the most frequently targeted structure, and treatment often yields improvements in multiple movement-related symptoms when electrodes are placed in the dorsolateral aspect of this structure.

Despite successful symptom reduction, STN stimulation is somewhat limited by a relatively low threshold for the production of such side effects as dysarthria, tonic muscle contraction, paresthesias, and eye deviation.21 Stimulation of surrounding anisotropic fiber tracts is thought to be responsible for these effects. For instance, ascending lemniscal fibers pass posterior to the STN whereas corticospinal and corticobulbar tracts of the internal capsule pass lateral, anterior, and inferior to it.6 While the dorsolateral portion of the STN represents sensorimotor functions, the medial and ventral regions are related to cognitive and emotional functions with possible mood changes, depression, or hypomania upon high-frequency stimulation. Thus, depending on the anatomical structure of individual patients, various side effects can be elicited if electrical current spreads significantly outside the dorsolateral STN.

Two common types of eye deviation have been described in association with STN stimulation: 1) Skewed eye deviation results in double vision with stimulation from contacts placed too medially. The electrical field is believed to activate oculomotor nerve fibers that course laterally along the border of the red nucleus before curving medially to exit the mesencephalon in the interpeduncular fossa. 2) Contralateral conjugate eye deviation is noted in certain patients. The mechanism of this effect is poorly understood, but some researchers have speculated that lateral placement of the electrode may result in activation of specific descending tracts within the internal capsule en route
to the medial pontine tegmentum nuclei for conjugate horizontal eye movements.\textsuperscript{8,9} The specific electrode placement site that can result in conjugate eye deviation is at present unknown. Thus, within a group of patients undergoing STN stimulation for PD, the precise contact locations resulting in contralateral eye deviation were compiled and analyzed as described below.

**Clinical Material and Methods**

Appropriate consent for data analysis was obtained from patients at the University of California at Los Angeles Medical Center, who were undergoing routine STN deep brain stimulation for PD symptoms after failure of medical therapy. From September 1999 through January 2004, 53 patients underwent placement of 97 STN-targeted electrodes. Contralateral eye deviation was noted with stimulation of 22 contact sites in nine of these patients. Each underwent standardized presurgical planning and electrode placement as follows: On the date of surgery, a Leksell stereotactic model G frame was placed for guidance. Magnetic resonance images were obtained in a 1.5-tesla Siemens MR imaging operating room suite with the stereotactic frame in place, allowing preparation of STN target coordinates using a BrainLAB iPLAN system. The STN trajectory was based on a measured AC–PC distance specific to each patient. A NeuroTrek (Alpha Omega, Ltd.) micro-electrode recording system was used to define the STN borders.

A deep brain stimulator lead (model 3389, Medtronic) was then inserted lateral to the midline and anterior to the coronal suture into each cerebral hemisphere on the basis of planned trajectory targets. After the patients were awakened for interrogation of each contact, monopolar stimulation with a mean voltage of 3.4 \( \pm 1.1 \) V (frequency 160 Hz, pulse width 90 msec) delivered to specific contacts resulted in contralateral conjugate eye deviation whereby patients could not volitionally move their eyes until electrical stimulation was discontinued. Final electrode placement was confirmed by a second MR imaging study immediately following skin closure. The electrode tip position was plotted using images from this study and BrainLAB iPLAN software. After accounting for changes in position during the surgery, the site of each contact that resulted in eye deviation was calculated relative to the AC–PC midpoint.

The lateral position of each contact relative to the commissural midline (x axis) was calculated with the contact lengths (1.5 mm) and intracontact spaces (0.5 mm) used to determine the midpoint of each contact. Considering each electrode as the hypotenuse of a right-angle triangle, Pythagorean relations allowed us to calculate each contact midpoint by multiplying the distance of each contact from the tip by the sine of the Leksell angle. Similarly, we calculated the position of each contact relative to the AC–PC plane along the z axis by multiplying the midpoint–tip distance by the cosine of the Leksell arc angle. The anteroposterior (y axis) coordinate of each contact was calculated by multiplying the midcontact–tip distance by the sine of the Leksell ring angle. Thus, based on the confirmed final position of each electrode, precise coordinates (x, y, and z) of each contact midpoint were ascertained. The mean values and SDs of the three contact coordinates were then determined in all patients.

**Results**

Acute-onset contralateral eye deviation was noted upon intraoperative stimulation of 22.7\% of the 97 electrodes placed in 53 patients. Nine patients (17.0\%) were noted to have this symptom before any other effects were observed as voltages were increased during intraoperative testing. Two patients demonstrated this response with stimulation of only one contact (Contact 1), whereas in other patients eye deviation was noted in association with stimulation of two (four patients) or three (three patients) contacts per side (Table 1). Threshold voltages for this side effect ranged from 1.0 to 4.8 V. If stimulation of an electrode with voltages lower than 4.0 V produced any side effects such as eye deviation, the electrode was repositioned to avoid this response upon chronic stimulation. As a result, eye deviation was only observed intraoperatively. At outpatient follow-up visits for stimulator adjustment, no chronic eye deviation responses were noted. Conjugate eye deviation was not produced in most patients in this study in the surgical or outpatient setting, even at higher voltages, as other side effects such as facial pulling were observed—requiring testing at lower voltages or electrode repositioning.

Conjugate eye deviation tended to be observed with stimulation of contacts closer to the electrode tip. The voltage threshold for eye deviation between adjacent contacts did not change in a consistent manner when compared across all patients. In one patient this side effect was observed in association with both the right and left electrodes, but in all other patients it was localized to one side. No significant effect was observed for laterality in the group as a whole.

The mean midcontact x coordinate responsible for contralateral eye deviation was found to be 11.57 mm (± 1.32 mm, SD) lateral to the coronal commissural midline. The mean y and z coordinates were 2.03 mm (± 1.76 mm) posterior to the AC–PC midpoint and 3.83 mm (± 3.52 mm) inferior to the AC–PC plane, respectively.

Thus, the convergence of these mean coordinates yields a point within the lateral anterosuperior border of the STN (Fig. 1). The SDs for the lateral and posterior coordinates are less than 2 mm each, whereas the SD of the inferior coordinates was at least double this value, suggesting there is more coordinate variability along the z axis.

**Discussion**

High-frequency stimulation may elicit effects on surrounding brain structures by activating neuronal elements within the electrical field that override the pathological activity of the target or by generating a functional ablation by inhibiting the stimulated target. The findings of recent studies have supported the former concept, as the electrical field produced in surrounding brain structures has become better understood.\textsuperscript{11} Electric fields are dependent on the shape of the electrode and electrical conductivity of the surrounding tissue.\textsuperscript{12} Monopolar stimulation generally produces electrical lines of force that radiate in all directions away from the cathode contact, with an ionic concentration...
Conjugate eye deviation with deep brain stimulation of the STN

TABLE 1
Threshold voltages resulting in conjugate eye deviation during intraoperative stimulation*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Side</th>
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<th>Voltage (V)</th>
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<td>1</td>
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* Contacts are numbered based on their distance from the electrode tip, with Contact 0 being nearest to and Contact 3 most distant from the tip in each case.

During microelectrode recording, high amplitude spikes at 25 to 45 Hz, consistent with STN electrical activity, are detected over a distance of approximately 4 mm, suggesting that all four contacts (7.5 mm) of the 3389 electrode are not placed within the STN borders. Previous studies have demonstrated the effective current spread from each contact projects outward approximately 3 mm at voltages similar to those in this study. Using diffusion tensor MR data, electrical spread outside the borders of the dorsolateral STN has been projected to activate axons in the zona incerta, the field H2 of Forel, and the internal capsule.

The location of our mean coordinate point suggests that stimulation of axonal projections from the substantia nigra pars reticulata to the superior colliculus is unlikely to produce the side effects noted in these patients. Furthermore, superior colliculus stimulation results in ocular motions with varying degrees of vertical displacement, which were not observed in the current study. Stimulation of nearby optic tract axons can result in the subjective experience of flashes of light but no extraocular motion disturbances.

**Fig. 1.** Schematic illustration showing the area within the lateral anterosuperior border of the STN identified by the mean coordinates of the locations that produced conjugate eye deviation upon stimulation. The right medial internal capsule is within 3 mm of the distal contact as indicated by concentric circles representing electrical current spread. **Insets A, B, and C:** The electrode trajectory in a representative patient is shown in coronal (A), sagittal (B), and axial (C) MR images. AL = ansa lenticularis; FL = fasciculus lenticularis; GPe = globus pallidus externus; GPi = globus pallidus internus; IC = internal capsule.
Thus, conjugate eye deviation is probably best explained by electrical current spread to internal capsule axons from the FEFs. The observed eye movements were similar to those described with frontal lobe epileptic seizures and frontal subdural stimulation electrodes.\textsuperscript{2,22} Transcranial magnetic stimulation and functional MR imaging studies have recently confirmed FEF involvement with intentional saccades, pursuit eye movements, and optokinetic nystagmus.\textsuperscript{15}

Conjugate horizontal gaze is characterized both by rapid saccadic eye movements for placement of visual objects of interest on the retinal fovea and by slower pursuit eye movements for object tracking. Examples of conjugate saccadic horizontal eye movements occur with physiological FEF excitation, vestibular ocular reflex, and optokinetic nystagmus. The FEF cortical neuronal projections are located in the caudal portion of the middle frontal gyrus at the base of the sulcus (Brodmann Area 8). As a central relay for volitional saccadic conjugate horizontal eye movements, the FEF receives multiple cortical inputs that initiate activation of the FEF neuronal pool.\textsuperscript{4,12,14} Primate studies have demonstrated visual cortex projections to the ipsilateral parietal cortex in relation to visualized motions and to the ipsilateral posterior middle temporal cortex regarding form and color characteristics (Fig. 2). Both of these associative visual cortices project to the FEF wherein cortical cognitive and reflexive inputs initiate volitional responses. In addition, FEF structural integrity and physiological activation are essential for the saccadic brainstem vestibular ocular reflex. During sleep or coma, an inactive FEF results in an absence of the saccadic phase upon caloric stimulation of the vestibular system.\textsuperscript{12,14,16}

The FEF neurons project to the PPRF, striatum, thalamus, and ipsilateral SC.\textsuperscript{12,14} The FEF tract decussates at the mesencephalic–pontine junction before innervating the contralateral PPRF. Thus, the conjugate horizontal gaze is opposite to the cortical FEF activated (Fig. 3).\textsuperscript{12,14} Both FEF and SC projections to the PPRF are required to accomplish normal horizontal conjugate saccadic eye movements because the basal ganglia and cerebellum modulate saccadic eye movements, but do not initiate them. The FEF direct (FEF to SC) and indirect pathways (FEF to caudate to globus pallidus/substantia nigra reticularis to SC) project to the superficial strata of the SC (stratum zonale, stratum optica, and stratum cinereum) before reaching the intermediate depth (stratum lemnisci).\textsuperscript{12,14} The stratum lemnisci projects to the PPRF and contributes to horizontal eye movement. Cerebral and cerebellar projections to the SC are also relayed to the rostral interspathus of medial longitudinal fasciculus nucleus for vertical eye movements.\textsuperscript{12,14} This pathway did not appear to be affected by high-frequency stimulation along the electrode trajectory, because no vertical eye deviation was noted.

Within the PPRF complex, saccadic eye movements are modulated by omnipause, excitatory burst, and inhibitory burst neurons.\textsuperscript{12,14} The FEF projections activate inhibitory interneurons that connect via synapses with omnipause neurons, located in the raphe interpositus. At rest the omnipause neurons are inhibitory to the excitatory burst and inhibitory burst neurons (located in the nucleus reticularis pontis caudalis and nucleus paragigantocellularis dorsalis, respectively). The excitatory burst neurons excite the ipsilateral sixth cranial nerve motor neurons that innervate the lateral rectus. The inhibitory burst neurons inhibit the ipsilateral third cranial nerve motor neurons and ipsilateral medial rectus via the medial longitudinal fasciculus (antagonistic to the ipsilateral horizontal saccade). Thus, activation of an inhibitory interneuron suppresses omnipause neuron inhibition of excitatory and inhibitory burst neurons—that is, it results in disinhibition (Fig. 4). This facilitates activation of the ipsilateral lateral rectus by excitatory burst neurons and inhibition of the ipsilateral medial rectus by inhibitory burst neurons. The converse occurs on the opposite side via the medial longitudinal fasciculus, resulting in conjugate horizontal eye movements opposite to the FEF initially activated.\textsuperscript{12,14}

None of the patients described in this study manifested contralateral upper extremity movements. This finding suggests that FEF projections are medial within the internal capsule relative to the cortical motor neuron projections ultimately activating spinal motor units to the upper extremity. Likewise, authors of previous studies have described descending cortical FEF fibers along the ipsilateral posterior or aspect of the internal capsule anterior limb and medial portion of the ipsilateral cerebral peduncle.\textsuperscript{1} Our results also demonstrate greater coordinate variability in the z axis, which corresponds to the trajectory of the internal capsule fibers as they travel inferiorly.

Conclusions

Contralateral conjugate eye deviation is produced in some patients undergoing STN deep brain stimulation. The mean coordinates calculated in this study indicate that electrode placement within the lateral anterosuperior border of the STN is most often responsible for this side effect. Instead of direct STN stimulation, electrical current spread to nearby FEF axons within the internal capsule is likely to be responsible for conjugate eye deviation. The lack of contralateral arm movement or vertical eye deviation supports a medial topology of the FEF projections within the internal capsule. It is possible that these findings are not observed in most patients with PD until after other motor symptoms are produced (with subsequent cessation of stimulation) because only a small number of FEF axons are
Fig. 3. The FEF tracts decussate at the mesencephalic–pontine junction before innervating the contralateral PPRF. Activation of the PPRF results in contralateral lateral rectus (LR) activation with concomitant contralateral medial rectus (MR) inhibition. The opposite occurs on the ipsilateral side via the medial longitudinal fasciculus (MLF), resulting in conjugate horizontal eye movements opposite to the FEF initially activated. Findings in this study support a medial location for FEF projections within the internal capsule. CN = cranial nerve.

Fig. 4. Within the left PPRF, an excitatory burst neuron (EBN) excites left-sided sixth cranial nerve motor neurons (lateral rectus) while an inhibitory burst neuron (IBN) inhibits left-sided third cranial nerve motor neurons (medial rectus) via the medial longitudinal fasciculus. Therefore, activation of an inhibitory interneuron suppresses omnipause neuron (OMP-N) inhibition of EBN/IBN, with resulting EBN activation of the lateral rectus and IBN inhibition of the medial rectus.
located in the internal capsule relative to the number of axons of major corticospinal projections. If eye deviation is noted, placement of the implanted electrode in a more medial, posterior, and inferior position may bring resolution of these symptoms by reducing the amount of current spread to internal capsule axons.

Disclaimer
The authors report no conflicts of interest.

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Address reprint requests to: Dr. Antonio A. F. DeSalles, Box 957182, Suite 504, 200 Medical Plaza, University of California at Los Angeles Medical Center, Los Angeles, California 90095-7182.
email: adesalles@mednet.ucla.edu.